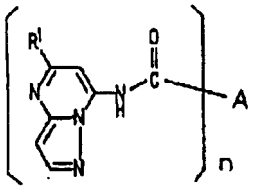
(Abstract)

Object

To put forward a novel compound having analgesic action, nitric oxide synthase inhibitory action or the like.

Method of Solution

It is a carboxamide derivative represented by general formula (1)



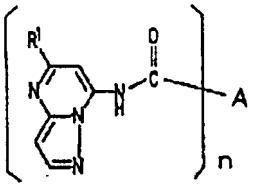
(1)

(wherein, R1 denotes a lower alkyl group, n denotes 2 or 3, and when n is 2, A denotes a single bond, lower alkylene group, benzene ring or naphthalene ring and when n is 3, A denotes a benzene ring or naphthalene ring).

Patent Claims

Claim 1

A carboxamide derivative represented by general formula (1)



(1)

(wherein, R1 denotes a lower alkyl group, n denotes 2 or 3, and when n is 2, A denotes a single bond, lower alkylene group, benzene ring or naphthalene ring and when n is 3, A denotes a benzene ring or naphthalene ring).

Claim 2

A carboxamide derivative in accordance with Claim 1, wherein when n is 2, A denotes a single bond, lower alkylene group, benzene ring or naphthalene ring, and when n is 3, A denotes a benzene ring.

Claim 3

A carboxamide derivative in accordance with Claim 2, wherein R1 is n-butyl group.

Claim 4

A carboxamide derivative in accordance with Claim 3, wherein n is 2.

Claim 5

A carboxamide derivative in accordance with Claim 4, wherein A is lower alkylene group or benzene ring.

Claim 6

A carboxamide derivative in accordance with Claim 5 comprising N,N'-bis (5-n-butyl pyrazolo[1,5-a]pyrimidine-7-yl)-1,4-benzene dicarboxamide or N,N'-bis (5-n-butyl pyrazolo[1,5-a]pyrimidine-7-yl) hexane diamide.

Detailed Description of the Invention

(0001)

Technical Sphere of the Invention

This invention relates to the following, namely, the novel carboxamide derivative having analgesic action, nitric oxide synthase inhibitory action or the like.

(0002)

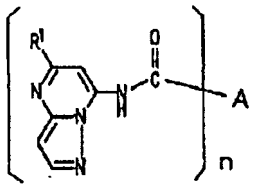
Technology of the Prior Art and Problems to be Overcome by this Invention

This invention has an object of putting forward novel compound containing analgesic action, nitric oxide synthase inhibitory action or the like which had been unmentioned in the literature.

(0003)

Means to Overcome these Problems

This invention puts forward a novel carboxamide derivative represented by general formula (1)



(1)

(wherein, R1 denotes a lower alkyl group, n denotes 2 or 3, and when n is 2, A denotes a single bond, lower alkylene group, benzene ring or naphthalene ring and when n is 3, A denotes a benzene ring or naphthalene ring).

The aforesaid A is preferred to be a single bond, lower alkylene group, benzene ring or naphthalene ring when n is 2, and benzene ring when n is 3. In such case, R1 is preferred to be n-butyl group.

(0004)

More preferably, A is lower alkylene group or benzene ring when n is 2. As embodiment, N,N'-bis (5-n-butyl pyrazolo[1,5-a]pyrimidine-7-yl)-1,4-benzene dicarboxamide and N, N'-bis (5-n-butyl pyrazolo[1,5-a]pyrimidine-7-yl) hexane diamide may be proposed. Such compounds of this invention (1) have analgesic action, nitric oxide synthase inhibitory action or the like. Accordingly compounds of this invention (1) are effective for relaxation of postoperative pain, migraine headache, gout, chronic pain, neurogenic claim(sic) pain, cancerous pain or the like as a analgesic, and it has the characteristic that it is almost free from the side effects which are common in prior art analgesics.

(0005)

Moreover, because the compounds of this invention (1) have the action of selectively inhibiting inducible-type nitric oxide synthase, as inhibitor of the said synthase, the said compounds will be effective for prevention and treatment of for example septicemia, endotoxin shock, chronic rheumatism and the like.

(0006)

Conditions for Carrying out this Invention

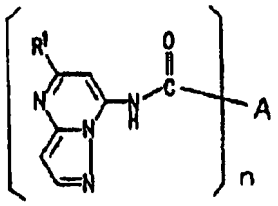
In accordance with this invention, as the aforesaid lower alkyl group, for example straight or branched lower alkyl group of carbon number 1-6 such as methyl, ethyl, propyl, isobutyl, tert-butyl, pentyl, hexyl group and the like may be proposed. As lower alkylene group, for example straight or branched lower alkylene group of carbon number 1-6 such as methylene, ethylene, ethylidene, trimethylene, methylethylene, tetramethylene, pentamethylene, hexamethylene group and the like may be proposed. Moreover, in compounds of this invention (1), the case wherein n is 2 and A is single bond denotes the case wherein the carbonyl groups in two carboxamide residues (-HNCO-) are directly-bonded.

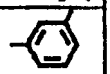
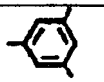
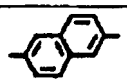
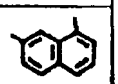
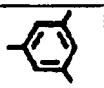
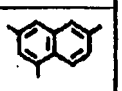
(0007)

Examples of carboxamide derivatives (1) of this invention are shown in Table 1 and 2. In each Table, Me; methyl group, Et; ethyl group, n-Pr; n-propyl group, n-Bu; n-butyl group, n-Pe; n-pentyl group, n-Hx; n-hexyl group is denoted respectivelly.

(0008)

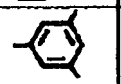
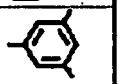
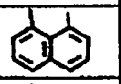
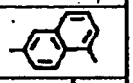
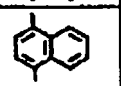
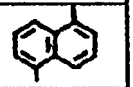
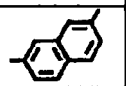
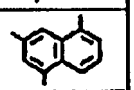
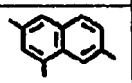
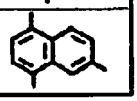
Table 1



R^1	n	A	R^1	n	A
Me	2		Et	2	
Me	2	Single bond	Et	2	Single bond
Me	2	$-(CH_2)_4-$	Et	2	$-(CH_2)_4-$
Me	2		Et	2	
Me	2		Et	2	
Me	3		Et	3	
n-Hx	2		n-Bu	2	$-CH_2-$
n-Hx	2	Single bond	n-Bu	2	CH_3 | $-CH-CH_2-$
n-Hx	2	$-(CH_2)_4-$	n-Bu	2	$-(CH_2)_6-$
n-Hx	2		n-Bu	2	
n-Hx	2		n-Bu	2	
n-Hx	3		n-Bu	3	

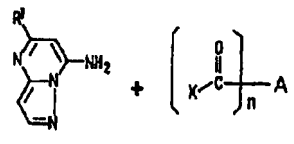
(0009)

Table 2

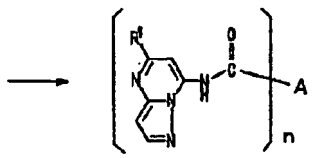
R^1	n	A	R^1	n	A
n-Pr	2		n-Pe	2	
n-Pr	2	Single bond	n-Pe	2	Single bond
n-Pr	2	$-(CH_2)_4-$	n-Pe	2	$-(CH_2)_4-$
n-Pr	2		n-Pe	2	
n-Pr	2		n-Pe	2	
n-Pr	3		n-Pe	3	
n-Bu	2	$-(CH_2)_2-$	n-Bu	2	$-CH(CH_3)-$
n-Bu	2	$-(CH_2)_3-$	n-Bu	2	$-(CH_2)_5-$
n-Bu	2		n-Bu	2	
n-Bu	2		n-Bu	2	
n-Bu	2		n-Bu	3	
n-Bu	3		n-Bu	3	

(0010)

The compound of this invention (1) can be produced according to the following reaction step equation.



(2) (3)



(wherein, R1, n and A are the same as above, and X denotes a halogen atom).

(0011)

In other words, compounds of this invention (1) can be produced by reacting compound (2) with acid halide (3). This reaction is preferably carried out in the presence of deoxidizer in a suitable solvent. As solvent, aromatic system or aliphatic system hydrocarbons such as benzene, toluene, xylene, light petroleum and the like, chain-form or cyclic ethers such as diethyl ether, dimethoxyethane, tetrahydrofuran (THF), 1,4-dioxane and the like, ketones such as acetone, ethyl methyl ketone, acetophenone and the like, halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-chloroethane and the like may be proposed.

(0012)

Moreover, as far as aforesaid deoxidizer is concerned, for example tertiary amine species such as triethylamine, N,N-diethylaniline, N-methylmorpholine, pyridine, 4-dimethylaminopyridine and the like, alkali metal hydride such as sodium hydroxide, potassium hydroxide and the like may be proposed. The quantities of acid halide (3) and deoxidizer used with respect to compound (2) in the aforesaid reaction are not restricted in particular, however usually it is preferably 1 – slightly in excess of equivalent amount of acid halide (3) and 1 - excess equivalent of deoxidizer with respect to compound (2). The reaction is preferably carried out under the temperature condition in a range of room temperature to the reflux temperature for about 0.5-20 hours.

(0013)

The target compound obtained by the aforesaid reaction can be readily isolated and purified by ordinary separation means. As such separation means, for example absorbent chromatography, preparative thin layer chromatography, recrystallization, solvent extraction and the like may be proposed. The compounds of this invention (1) can be made into the pharmacologically acceptable acid addition salt, and such salts are included in this invention, too. As acid forming the aforesaid acid addition salt, inorganic acid such as hydrochloric acid, hydrobromic acid, sulfuric acid or the like, organic acid such as oxalic acid, fumaric acid, maleic acid, tartaric acid, citric acid, p-toluenesulfonic acid or the like may be proposed. The formation of acid addition salt can be carried out in accordance with normal methods.

(0014)

Moreover, the compounds of this invention can be also made into alkali metal salt such as sodium salt, potassium salt and the like, alkaline earth metal salt such as calcium salt, magnesium salt and the like and moreover cuprates according to normal method, and these salts are included in this invention, too. The compounds of this invention (1) are used by forming into a general drug preparation by using together with suitable non-toxic preparation carrier. As the aforesaid preparation carrier, excipient, diluent and the like such as filler, expander, binding agent, humectant, disintegrating agent, surface active agent, lubricant and the like, which is conventionally used corresponding to use conditions of preparation may be proposed, and these are suitably selected corresponding to administration unit form of the obtained preparation, and used.

(0015)

As administration unit form of the drug preparation of the compounds of this invention (1), various forms can be selected corresponding to therapy object, and as representative examples thereof, tablet, pill, powder, liquid agent, suspending agent, emulsion, granule, encapsulated formulation, suppository, injection (liquid agent, suspending agent), ointment and the like may be proposed.

(0016)

When forming into tablet, as the aforesaid preparation carrier, for example excipient such as lactose, refined sugar, sodium chloride, glucose, urea, starch, calcium carbonate, kaolin, crystalline cellulose, silica, potassium phosphate and the like; binding agent such as water, ethanol, propanol, single syrup, glucose liquid, starch liquid, gelatin solution, carboxymethylcellulose, hydroxypropylcellulose, methyl cellulose, polyvinylpyrrolidone and the like; disintegrating agent such as carboxymethylcellulose sodium, carboxymethylcellulose calcium, low degree of substitution hydroxypropylcellulose, dry starch, sodium alginate, agar powder, laminaran powder, sodium bicarbonate, calcium carbonate and the like; surfactant such as polyoxyethylene sorbitan fatty acid esters, sodium lauryl sulfate, stearic acid monoglyceride and the like; disintegration inhibitor such as refined sugar, stearin, cacao butter, hydrogenated oil or the like; adsorption enhancer such as quaternary ammonium salt group, sodium lauryl sulfate and the like; moisture retaining agent such as glycerol, starch and the like; adsorbent such as starch, lactose, kaolin, bentonite, colloidal silica or the like; lubricant such as purified talc, stearate, boric acid powder, polyethyleneglycol and the like can be used.

(0017)

Further the tablet can be made into the tablet coated with ordinary agent coating in accordance with requirements, for example sugar coated tablet, gelatin encapsulation tablet, enteric coated tablet, film coating tablet or double tablet, multilayer tablet. When formed into the form of a pill, excipient such as for example carrier such as glucose, lactose, starch, cacao butter, hardened vegetable oil, kaolin, talc and the like; binding agent such as powdered gum arabic, tragacanth powder, gelatin, ethanol and the like; disintegrating agent such as laminaran, agar and the like can be used as preparation carrier.

(0018)

When formed into a form of suppository, as preparation carrier, for example polyethyleneglycol, cacao butter, higher alcohol, esters of higher alcohol, gelatin, semi-synthetic glyceride and the like can be used. Encapsulated formulation is usually prepared according to normal method, by mixing compounds of this invention (1) with the various preparation carrier exemplified above and packing into hard gelatin capsule, soft capsule and the like.

(0019)

When prepared as injection agent such as liquid agent, emulsion, suspension and so on, such materials are sterilized and preferably made isotonic with blood. For the preparation of injection, as a diluent, for example, water, ethanol, macrogol, propylene glycol, ethoxylation isostearyl alcohol, polyoxyisosteary alcohol, polyoxyethylene sorbitan fatty acid ester species as can be used. Moreover, in this case, sufficient sodium chloride, dextrose or glycerol to form an isotonic solution may be contained in agent of this invention, and moreover ordinary solubilizer, buffer agent, analgesic or the like may be added. Furthermore, in agent of this invention, colorant, preservative, odorant, flavor agent, sweetener and so on and other pharmaceutical can be contained in accordance with requirements.

(0020)

When prepared into a form of ointment such as paste, cream, gel and the like, for example white petrolatum, paraffin, glycerol, cellulose derivative, polyethyleneglycol, silicone, bentonite and the like can be used as diluent. The amount of compounds of this invention (1) to be contained in the agent of this invention is suitably selected from a wide range without restriction in particular, but usually one containing an amount of about 1-70 wt.% approximately in the drug preparation is satisfactory.

(0021)

Administration method of the drug preparation of this invention is not limited in particular, and it is determined corresponding to various formulations, age of patient, the distinction of sex, other conditions, degree of disease or the like. For example, tablet, pill, liquid agent, suspension, emulsion, granule and encapsulated formulation are administered orally, and injection is used alone or mixed with ordinary adjuvant fluid such as dextrose, amino acid or the like, and administered intravenously, and further it is administered alone intramuscularly, intracutaneously, subcutaneously or intraperitoneally in accordance with requirements, and, the suppository is administered rectally. The dose of the aforesaid drug preparation is suitably selected by using the method of use thereof, age of patient, the distinction of sex, other conditions, degree of disease or the like, but usually the amount of the effective ingredient compounds of about 0.5-20 mg, preferably 1-10 mg per 1 kg bodyweight per day is satisfactory, and said preparation can be administered by being divided 1-4 times per day.

(0022)

Examples

Below the compounds of this invention are described in greater detail by reference to Examples and Test Examples.

Example 1

Production of N,N'-bis (5-n-butyl pyrazolo[1,5-a]pyrimidine-7-yl)-1,4-benzene dicarboxamide.

Terephthalic acid 0.83 g was dissolved in chloroform 5 mL, and thionyl chloride 1.43 g and N,N-dimethylformamide 0.22 g were added, and the mixture was stirred at room temperature for one hour, and then at 80°C for four hours, and thereafter it was concentrated under reduced pressure, and terephthaloyl chloride was obtained. The obtained terephthaloyl chloride was dissolved in dichloromethane 10 mL and pyridine 10 mL, and thereto was added 7-amino-5-n-butyl pyrazolo[1,5-a]pyrimidine 1.90 g under ice cooling, and thereafter the mixture was stirred at 0°C for one hour and then at room temperature for 15 hours. The reaction liquor was transferred to separatory funnel, and it was washed successively with dilute hydrochloric acid, sodium hydroxide aqueous solution and water, and after drying with anhydrous sodium sulphate, concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluate; chloroform : methanol = 10 : 1) and it was further recrystallised from chloroform-n-

hexane, and crystalline 1.38 g of the target compound was obtained. The structure and mp. of this compound are shown in Table 3.

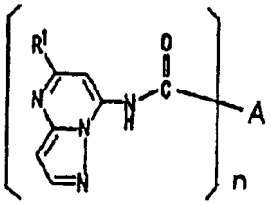
(0023)

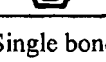
Examples 2-6

Using suitable starting material, each compound having structure and mp. shown in Table 3 was produced in the same way as in aforesaid Example 1. In Table 3, n-Bu denotes n-butyl group.

(0024)

Table 3



Example No.	R^1	n	A	mp. (°C)/recrystallisation solvent
1	n-Bu	2		234~236 chloroform - n-hexane
2	n-Bu	2	Single bond	214~216 chloroform - n-hexane
3	n-Bu	2	$-(CH_2)_4-$	195~197 chloroform - n-hexane
4	n-Bu	2		142~144 chloroform - n-hexane
5	n-Bu	2		258~260 chloroform - n-hexane
6	n-Bu	3		266~268 chloroform - n-hexane

(0025)

The NMR measurement results of the obtained each compound are shown below.

Compound of Example 1

^{1}H-NMR ($CDCl_3$) δ : 0.99 (6H, t, J = 7.4), 1.4-1.5 (4H, m), 1.7-1.9 (4H, m), 2.89 (4H, t, J = 7.9), 6.62 (2H, d, J = 2.5), 7.77 (2H, s), 8.06 (2H, d, J = 2.5), 8.2-8.3 (4H, m), 10.14 (2H, brs).

Compound of Example 2

^{1}H-NMR ($CDCl_3$) δ : 0.98 (6H, t, J = 7.4), 1.4-1.5 (4H, m), 1.7-1.9 (4H, m), 2.89 (4H, t, J = 7.7), 6.63 (2H, d, J = 2.5), 7.63 (2H, s), 8.10 (2H, d, J = 2.5), 11.04 (2H, brs).

(0026)

Compound of Example 3

^{1}H-NMR ($CDCl_3$) δ : 0.95 (6H, t, J = 7.3), 1.3-1.5 (4H, m), 1.7-1.8 (4H, m), 1.9-2.0 (4H, m), 2.6-2.7 (4H, m), 2.81 (4H, t, J = 7.8), 6.55 (2H, d, J = 2.2), 7.60 (2H, s), 7.99 (2H, d, J = 2.2), 9.26 (2H, brs).

Compound of Example 4

^{1}H-NMR ($CDCl_3$) δ : 0.99 (6H, t, J = 7.4), 1.4-1.5 (4H, m), 1.7-1.9 (4H, m), 2.89 (4H, t, J = 7.9), 6.61 (2H, d, J = 2.5), 7.79 (2H, s), 7.81 (1H, t, J = 7.9), 8.06 (2H, d, J = 2.5), 8.29 (2H, d, J = 7.9), 8.73 (1H, s), 10.16 (2H, brs).

(0027)

Compound of Example 5

^{1}H-NMR ($CDCl_3$) δ : 0.99 (6H, t, J = 7.3), 1.4-1.6 (4H, m), 1.7-1.9 (4H, m), 2.90 (4H, t, J = 7.9), 6.62 (2H, d, J = 2.5), 7.81 (2H, s), 8.09 (2H, d, J = 2.5), 8.1-8.3 (4H, m), 8.61 (2H, s), 10.22 (2H, brs).

Compound of Example 6

^{1}H-NMR ($CDCl_3$) δ : 0.99 (9H, t, J = 7.3), 1.4-1.5 (6H, m), 1.7-1.9 (6H, m), 2.89 (6H, t, J = 7.8), 6.60 (3H, d, J = 2.4), 7.77 (3H, s), 8.04 (3H, d, J = 2.4), 8.94 (3H, s), 10.27 (3H, brs).

(0028)

Test Example 1

Analgesic active test of carboxamide derivative (1)

Using 7 animals per group of 6-week old S.D. strain male rat, firstly, pain threshold of left posterior limb footpad of each rat was measured in accordance with Randall • Sellitto method (Randall. L.O. and Sellitto, J.J, Arch, Int, Pharmcodyn, 111, 409 (1957)) using pressure stimulation analgesia effect measuring apparatus (made by Unicom Co.). The obtained value is called "the earlier value". One hour after the measurement of the aforesaid earlier value, 5 % gum arabic suspension of test compound to experimental group and 5 % gum arabic suspension which does not include test compound to control group were respectively administered orally so as to become the proportion of 10 mL/kg

body weight (effective ingredient dose: 1 mg/kg body weight), and after further 1 hour, physiological saline solution of substance P (made by Sigma Corp.) (25 ng 0.1 ml) was injected to the left posterior limb footpad of each rat subcutaneously.

(0029)

Next, pain threshold of the left posterior limb footpad of each group rat was measured after prescribed time of substance P injection in the same way as described above, and it is called "the later value". The pain threshold recovery rate (%) was calculated according to the following equation from the later value and the earlier value of each group.

Equation 1

The pain threshold recovery rate (%) = (the later value of experimental group) - (the later value of control group) / (the earlier value of control group) - (he later value of of control group)

(0030)

The results (the maximum recovery rate) are shown in Table below.

Table 4

Example No.	Recovery rate (%)	The later value measurement time (minutes after)"
1	72.8	60
2	21.5	60
3	71.5	60
4	27.2	60
5	23.4	60

(0031)

Advantages Afforded by this Invention

The carboxamide derivative of this invention has the effect such as having an analgesic action and nitric oxide synthase inhibitory action.

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